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Developing Treatment, Treatment Validation, and Treatment Scope in the Setting of an Autism Clinical Trial

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14. ABSTRACT The second year of the project has been used to obtain IRB approval from the UMDNJ-RWJMS IRB office. We obtained IRB approval on December 7 th , 2009. Our approved protocol and supporting documents were submitted to the Human Research Protection Office (HRPO) Office of Research Protections (ORP) of the DOD for review. We applied for and received a Certificate of Confidentiality from the NIH as per our IRB requirements. The test material DHA and the placebo were acquired from Martek with a significant and unforeseen delay. (Please see Task #2 in this Document). Subject recruitment has been organized. A Continuing Review has been applied for. The Data Safety Monitoring Board (DSMB) has been set up and provided with necessary documents to hold their initial meeting with the exception of the CR which will be sent as soon as we receive. Human Subjects recruitment and tasks #3 through 7 will begin once the DSMB have given approval. We are in the process of arranging additional sources of ADOS and ADI tested subjects so that we can reach our recruitment goals more quickly. In addition, as originally designed samples from AGRE would be obtained by initiating project W81XWH-08-1-0728 for the relevant tasks of project W81XWH-08-1-0728. To simplify matters since the IRB approval is in Dr. Novotny's name this task was moved to this project (W81XWH-08-1-0730). We submitted a material transfer agreement and a formal application including the changes in the research design made in the last two quarters (detailed in initiating project W81XWH-08-1-0728 under Task 4) to AGRE. The application has been approved. Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.					
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Introduction:

This project is to test to see if DHA treatment can beneficially affect excretion of urinary biomarkers of oxidative stress and the autism clinical phenotype. In addition polymorphic variants of genes of certain enzymes that synthesize and metabolize docosahexaenoic acid (DHA) may contribute to the phenotype of some autism cases. We will test to see if any of these genes are risk factors for autism. We will also measure changes in excretion of the polyunsaturated fatty acid (PUFA) derived biomarkers of oxidative stress (isoprostanes and neuroprostanes) together with the changes in production of anti-inflammatory lipid mediators. We will test these biomarkers to see if we can monitor and validate effectiveness of DHA therapy. We will also test the genotypes of key DHA-metabolizing enzymes can predict which patients will respond to therapy.

Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.

Body:**Project 1: PI Sherie Novotny, MD, Partnering PI, W81XWH-08-1-0730**

Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.

Task 1 Full board review with pending IRB approval prior to beginning (4-6 months, S. Novotny).

IRB Approval has been obtained.

The months of October and November were used to answer additional IRB issues. We obtained IRB approval on December 7th 2009 with the stipulation that we apply to the NIH for a Certificate of Confidentiality (COC) and if/when we received it we would have to send in an amendment to our IRB. We sent the approved protocol and related documents to the Human Research Protection Office (HRPO), Office of Research Protections (ORP) of the DOD for review on December 10th 2009. We applied for the COC on December 15th, 2009. We received a COC March 2nd 2010. The COC and the requested changes received from the Human Research Protection Office (HRPO), Office of Research Protections (ORP) of the DOD on January 9th 2010 were submitted as an amendment to our IRB office on March 8th. This went for an expedited review and we were informed on March 25th that the amendment was accepted. All relevant documents were sent to the Human Research Protection Office (HRPO), Office of Research Protections (ORP) of the DOD on March 30th.

As per the request of the Human Research Protection Office (HRPO), Office of Research Protections (ORP) of the DOD we submitted an amendment to our IRB on July 6th 2010 to change the backup for Dr. Novotny from Dr. Petti to Dr. Lambert to avoid a potential conflict of interest. The amendment was approved on July 22nd 2010.

The protocol that was approved on December 7th 2009 had an expiration date of October 1st 2010. Therefore a continuing review was submitted. We were issued an approval pending 4 minor changes on October 4th.

Due to the fact that the IRB process took longer then expected the SOW was updated on March 22nd 2010.

Task 2 Volunteers recruited from local clinics, support groups and advocacy groups (6-30 months).Forty four child or adolescent outpatients per year with age ranges from 5-17, for three years totaling 132 patients, will be randomized into the 12-week double-blind, placebo-controlled parallel treatment study.

An unanticipated problem delaying recruitment was getting the DHA and Placebo from Martek so that we could start recruiting subjects. We submitted the fully approved protocol to the supplier of the DHA and Placebo Martek along with all relevant documents and medical licenses and a completed FDA form 1572 on April 1st 2010 as required by Martek to initiate a materials transfer agreement. On April 15th 2010 we received an e-mail from a Martek representative. They requested that we change our IRB protocol by significantly increasing the dosage to “maximize the chances of success”. We strongly disagreed with their suggestion and prepared and sent a response. The response was based on studies showing that too large a dose could change normal processing of DHA as well as excretion of biomarkers. A telemeeting was held between a representative from Martek and Mr. Stenroos on April 23d 2010. It was then agreed that our protocol was correct and acceptable. Martek then went to work on the material transfer agreement. We received the agreement on May 19th 2010. Upon review there were two items of concern. 1.) Martek was asking for all patent rights on the project. 2.) Martek was asking the University and therefore the State of NJ to take responsibility for insurance costs if there was an adverse effect. Naturally, neither of these items is acceptable to the University. We had a meeting with our lawyer responsible for negotiating this on May 27th 2010 and a follow up meeting to finalize the response on June 9th 2010. Our licensing department sent a reply on June 17th 2010. The response to the first item was to notify Martek what patents had previously been applied for, therefore indicating the University's ownership of Intellectual Property related to the project. In addition our licensing department suggested that all intellectual property solely developed by Martek should be patented by Martek, all intellectual property solely developed by us should be patented by us and all intellectual property developed together should be shared equally. The response to the second item was to notify Martek as to what is legal and acceptable to UMDNJ and the State of NJ. We received a response from Martek on July 20th . We received the final Materials Transfer agreement from Martek on August 4th . We returned the signed copy to Martek on August 9th . We received the DHA and Placebo August 20th .

Lists of subjects interested in participating in studies have been organized by contacting special schools, pediatricians, psychiatrists and special educators in the Middlesex County, where we are based, as well as the neighboring counties. Letters to these professionals have helped in bringing forward many potential subjects who have been contacting Dr. Novotny.

Recruitment letters have been written and are waiting IRB approval for both Dr. Lambert and Dr. Ming. Since the samples from Dr's Ming and Lambert were collected with approved protocols that allowed future use It was originally determined that the letters did not need to be reviewed by our IRB. We have since been informed that our IRB wants to review the two letters before they are sent out. Once approved they will send the letters to their subjects, recruited for pervious projects that expressed a wish to be informed about future projects. Since subjects from these sources have already undergone ADOS and ADI we will be able to save time in recruitment. In addition two other sources of ADOS and ADI tested subject recruitment are being investigated and once agreements are reached we expect to have access to about 100 more subjects. With these additional subjects we expect to be able to reach our recruitment goals quickly.

The medical monitor, Dr. Petti has been sent the approved protocol, consent and assent. He will be sent the Continuing review and copies of changed documents once we receive them.

The Data and Safety Monitoring Board (DSMB) has been set up. The members are Dr's Wei-Ting Hwang of UPenn, Kapila Seshadri of UMDNJ-RWJ and Bart Kamen of UMDNJ-RWJMS. Each has been given the approved protocol, consent and assent for review. Once the Continuing Review has been received it will be sent to the board with copies of the documents that were changed. Once this has been done the initial meeting of the DSMB will be held. This is to be done prior to the initiation of the trial as per the protocol. Once the board has met and given approval subject recruitment will begin.

As originally designed samples from AGRE would be obtained by initiating project W81XWH-08-1-0728 for the relevant tasks of project W81XWH-08-1-0728. To simplify matters since the IRB approval is in Dr. Novotny's name this task was moved to this project (W81XWH-08-1-0730). We submitted a material transfer agreement and a formal application including the changes in the research design made in the last two quarters (detailed in initiating project W81XWH-08-1-0728 under Task 4) to AGRE. The application was approved.

Task 3 Informed consent/assent obtained (6-30 months).

This task has not begun yet. This will start once recruitment starts.

Task 4 Full diagnostic assessment with Autism Diagnostic Interview-revised (ADI-R), Autism Diagnostic Observation Scale (ADOS), Vineland Adaptive behavior scale and Leiter Intelligence Scale (E Roberts); DSM IV criteria (S. Novotny) for eligibility & diagnosis. Parents will complete baseline Aberrant Behavior Checklist; study psychiatrist will complete Clinical Global Improvement, baseline Severity Scale (6-30 months).

This task has not begun yet. This will start once recruitment starts.

Task 5 Cases undergo full medical evaluation to determine health; at this visit will have phlebotomy including 10 mls for blood chemistry, PT/PTT, hematology, 10 ml for genotyping (Project III), urine for pregnancy test, drug screen as indicated, routine urinalysis; urine collected for Project II.

This task has not begun yet. This will start once recruitment starts.

Task 6 Cases randomized to receive either DHA, 200mg daily, or placebo. Cases given DHA after physical exam and routine lab-work completed.

This task has not begun yet. This will start once recruitment starts.

Task 7 Cases seen weekly for four weeks and biweekly for the remaining 8 weeks. Aberrant Behavior Checklist done every 4 weeks and at termination and Clinical Global Improvement Scale done every 2 weeks and at termination.

This task has not begun yet. This will start once recruitment starts.

Task 8 Cases complete the study with repeat ADOS, Vineland Adaptive Behavior Scale (E Roberts) and Aberrant Behavior checklist (parent) and Clinical Global Improvement Scale (S Novotny). Blood work for safety measures; urine will be collected for Project II during last week of DHA or placebo.

This task has not begun yet. This will start when treatment starts..

Task 9 Data will be collected and analyzed (6-36 months, S Buyske).

This task has not begun yet. This will start once when analysis of samples is completed.

Task 10 Manuscripts prepared and submitted for publication (03 year, all investigators)

This task is to be done when the analysis of the data is completed.

Key Research Accomplishments

There are no Key Research Accomplishments yet.

Reportable Outcomes:

There are no reportable outcomes for any of the three projects as of yet.

Conclusion:

A large amount of time was spent on getting IRB approval for this project. We received a conditional IRB approval on December 7th 2009. We applied for and received a COC from the NIH. We received full approval on March 25th, 2010. We had an unanticipated loss of time in obtaining the compound DHA and the placebo from the supplier Martek. Subject recruitment has been organized. A Continuing Review has been applied for. The Data Safety Monitoring Board (DSMB) has been set up and provided with necessary documents to hold their initial meeting with the exception of the CR which will be sent as soon as we receive. Human Subjects recruitment and tasks #3 through 7 will begin once the DSMB have given approval.

In addition, as originally designed samples from AGRE would be obtained by initiating project W81XWH-08-1-0728 for the relevant tasks of project W81XWH-08-1-0728. To simplify matters since the IRB approval is in Dr. Novotny's name this task was moved to this project (W81XWH-08-1-0730). We submitted a material transfer agreement and a formal application including the changes in the research design made in the last two quarters (detailed in initiating project W81XWH-08-1-0728 under Task 4) to AGRE. The application was reviewed and we are awaiting final release of samples from AGRE.

Once recruitment has started we will begin tasks 3 – 7. We anticipate no potential problems that would impede progress in recruiting the subjects. We expect that we can move forward rather quickly. We are setting up additional sources of ADOS and ADI tested subjects to allow recruitment to be done more quickly. In addition, we constantly receive phone calls from parents that would like to enroll their child in this study. In addition our past experience suggests that the parents of the individuals with autism will be eager to have their children participate in this project.

References:

There are no references.

Appendices:

There are no appendices.